

Prenatal Marijuana Exposure and Intelligence Test Performance at Age 6

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ABSTRACT

Objective: This is a prospective study of the effects of prenatal marijuana exposure on the intelligence test performance of 648 children at a 6-year follow-up. **Method:** Women were interviewed about the amount and frequency of their marijuana use at 4 and 7 months of pregnancy and at delivery. Participants were light to moderate users of marijuana and represented a lower income population. Children were assessed with the Stanford-Binet Intelligence Scale by examiners blind to exposure status. Multiple regression was applied to examine the effects of prenatal marijuana exposure on children's intelligence after partialing out the effects of other significant predictors. **Results:** There was a significant nonlinear relationship between marijuana exposure and child intelligence. Heavy marijuana use (one or more cigarettes per day) during the first trimester was associated with lower verbal reasoning scores on the Stanford-Binet Intelligence Scale. Heavy use during the second trimester predicted deficits in the composite, short-term memory, and quantitative scores. Third-trimester heavy use was negatively associated with the quantitative score. Other significant predictors of intelligence included maternal IQ, home environment, and social support. **Conclusions:** These findings indicate that prenatal marijuana exposure has a significant effect on school-age intellectual development. *J. Am. Acad. Child Adolesc. Psychiatry*, 2008;47(3):254–263. **Key Words:** cognitive ability, Stanford-Binet Intelligence Scale.

This study examines the effects of prenatal marijuana exposure (PME) on the children's intellectual development at age 6. The data are from the Maternal Health Practices and Child Development Project (MHPCD), a prospective study representing a low-income population. An earlier report from the MHPCD¹ showed that PME predicted lower scores on the verbal reasoning and short-term memory area scores of the Stanford-Binet Intelligence Scale (SBIS)² at age 3. This report investigates whether the effects of PME that were found

on intelligence at age 3 continued to be evident at age 6 years.

Animal studies show that cannabinoid exposure during gestation disrupts the ontogeny of the developing brain and modifies motor behavior and cognition among rodents.^{3–6} PME may target the cannabinoid receptor CB₁ present in the CNS, disrupting the regulation of neural development,⁷ including migration, differentiation,^{8–10} and synaptic communication.¹¹ Mereu and colleagues¹² found that prenatal exposure to a CB₁ receptor agonist caused memory deficits and hyperactive behavior among rats. The biological mechanism underlying the memory impairment was attributed to a decrease in hippocampal glutamate outflow. Thus, from animal studies, it is known that PME results in changes in brain development that have long-lasting consequences for cognitive function. The question is whether these adverse outcomes found in animals can be translated to intellectual deficits in humans.

In humans, reports of the effects of PME on child intelligence have been inconsistent. In the MHPCD study, PME predicted significantly lower scores on the

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Bayley Scales of Infant Development, Mental Development Index¹³ at 8 months of age.¹⁴ At 18 months of age, there were no effects of PME on this measure. At the 3-year follow-up, PME was a significant predictor of decreased SBIS verbal and short-term memory scores among the African American children and among white children who did not attend preschool/day care.¹

In the Ottawa Prenatal Prospective Study (OPPS), at 1 and 2 years of age, no relation was found between the Bayley Scales of Infant Development, Mental Development Index and PME.¹⁵ At age 3 in the OPPS, children exposed to more than five marijuana cigarettes per week during gestation had significantly lower quantitative scores on the McCarthy Scales of Children's Abilities¹⁶ compared with the rest of the cohort,¹⁷ but this difference was not significant after controlling for demographic variables. At 4 years, after adjusting for other risk factors, significant associations between PME and deficits in the McCarthy Scales of Children's Abilities verbal and memory subscales were found. At 5 and 6 years, there was no significant association between PME and cognitive functioning.¹⁸ Similarly, in a longitudinal study of rural Jamaican children,¹⁹ no significant differences were found between marijuana-exposed and -unexposed children on the McCarthy Scales of Children's Abilities at 4 and 5 years of age. Noland et al.²⁰ did not find an adverse effect of PME on executive functioning tasks at 4 years of age.

In the present study, the association between PME and child intelligence test performance at age 6 was examined. PME was measured at each trimester of pregnancy, and both timing and severity of exposure were considered. Other variables that influence child cognitive development such as familial socioeconomic status,²¹⁻²³ postnatal home environment,^{24,25} maternal intellectual ability,²⁶ social support,²⁷ and prenatal exposure to alcohol²⁸⁻³⁰ and tobacco¹⁷ were controlled for in the analyses. The effects of PME on child IQ were evaluated relative to the effects of other significant predictors.

METHOD

Study Design

Pregnant women who were at least 18 years of age and attended the prenatal clinic at the Magee-Womens Hospital were approached at their fourth prenatal month visit to enroll in the

MHPCD project, a study of the effects of prenatal marijuana and alcohol exposure. The project was approved by the institutional review boards of the Magee-Womens Hospital and the University of Pittsburgh. A total of 1,360 women were screened. All of the women who reported using two or more marijuana cigarettes per month during the first trimester of pregnancy, and all women who reported drinking three or more drinks per week during the first trimester were selected. After each marijuana and/or alcohol user was enrolled, a woman who reported using less than these amounts was also selected. Thus, the sample represents the continuum of marijuana and alcohol use. Information regarding marijuana, alcohol, tobacco, and other drug use during the first, second, and third trimesters of pregnancy was obtained at the fourth and seventh months of pregnancy and at delivery, respectively.

The MHPCD birth cohort consisted of 763 live singleton newborns. At 6 years, 668 subjects were interviewed, which represents 88% of the birth cohort. Subject losses between birth and 6 years were due to death of the child ($n = 4$), adoption ($n = 8$), family moved out of the state ($n = 41$), refusals ($n = 34$), and lost to follow-up ($n = 8$). Of the 668 subjects who were interviewed at the 6-year follow-up, 19 children with a physical or mental disability were excluded from the analyses, and 1 child was not tested. This report is based on 648 children. There were no significant differences in prenatal substance exposure or demographic characteristics between subjects included in this analysis ($n = 648$) and those who were not included ($n = 115$).

Characteristics of the Study Cohort

The maternal characteristics are listed in Table 1. At recruitment, most of the women had a high school education and were single. The MHPCD participants were generally of lower social status with a median monthly family income of \$350 at the first interview and \$900 at 6 years postpartum. Forty-seven percent of the women were white and the rest were African American.

The children were, on average, 6.5 years old (SD 0.5) at the 6-year assessment. The cohort was equally divided between males and females. Four percent of the children did not live with their biological mothers at the time of the interview. In these cases, the

TABLE 1
Maternal Characteristics

		Range
First trimester		
Age, y, mean	23.0	18-42
Education, y, mean	11.8	7-18
Race, % white	46.9	
Monthly family income, median ^a	\$350	\$0-1,000+
Married, %	32.1	
Work/school, %	26.8	
6 y		
Education, y, mean	12.2	7-20
Monthly family income, median	\$900	\$0-7,500
Married, %	35.0	
Work/school, %	66.5	
Estimated IQ ^b	88.5	58-122

^a Measured from 1982 to 1985.

^b Measured by the two-subtest version of the WAIS-R.³⁶

primary caregiver was interviewed. Approximately 55% of the children had a less optimal home environment, as defined by scores below 42 on the Home Screening Questionnaire.³¹ The children's mean SBIS composite score was 91.6, which is below the mean (100) of the standardization sample.

Measures

Maternal Substance Use. Prenatal marijuana use was measured based on the quantity and frequency of marijuana, hashish, and sinsemilla use for each month of the first trimester and across the second and third trimesters of pregnancy. Because the concentration of Δ -9-tetrahydrocannabinol in each substance differs, the quantities of hashish and sinsemilla were transformed into three and two marijuana cigarettes, respectively,^{32,33} and marijuana exposure was then expressed as the average daily "joints" (ADJ). The development of the MHPCD substance use questionnaire, ascertainment of pattern of use, duration and quantity of use, and methods to minimize recall error and maximize honest reporting are described in detail elsewhere.³⁴

Consumption of all types of alcoholic beverages was summed and average daily volume of alcohol use was calculated using the quantity and frequency of beer, wine, and liquor use during each trimester of pregnancy. A natural logarithm of average daily volume of alcohol use was used in these analyses to decrease skewness. Prenatal tobacco exposure was measured by the number of tobacco cigarettes smoked per day. Information regarding the quantity and frequency of cocaine use was also collected, but due to its low prevalence in this cohort, it was dichotomized to use (= 1) and no use (= 0) across pregnancy. At 6 years postpartum, maternal substance use was assessed for the preceding year, using the same questions as in the prenatal questionnaires.

Intelligence. The SBIS Fourth Edition² was used to measure the child's cognitive development at 6 years. The scale consists of four area subtests: verbal reasoning, quantitative reasoning, abstract/visual reasoning, and short-term memory. The abstract/visual reasoning subtest is referred to as fluid-analytic ability and requires cognitive skills to solve nonverbal novel tasks.² The verbal and quantitative reasoning subareas are referred to as crystallized intelligence³⁵ or scholastic abilities because they are influenced by schooling and rely on acquired knowledge. The composite score and the area subtests were standardized according to the child's age. For age 6, the composite score has an internal consistency reliability score of 0.96 and an SE of measurement of 3.2 points.²

Children were assessed by trained examiners who were blind to maternal prenatal and current substance use. The area scores and the total composite score were used in this analysis to examine whether the effects of prenatal exposure were specific to a certain domain of function.

Other Variables

Maternal cognitive ability was measured by the WAIS-R vocabulary and block design subtests.³⁶ Maternal psychological measures included depressive symptoms, using the Center for Epidemiological Studies-Depression Scale,³⁷ and hostility, assessed with the Spielberger State-Trait Anxiety Inventory.³⁸ Social environment was assessed with maternal variables, including the number of life events, the number of close relatives and friends, level of satisfaction with relatives' support (0 = very dissatisfied, 4 = very satisfied), and level of satisfaction with friends' help and support. Life events and social support were from the Psychiatric Epidemiology Research Interview Life Events Scale³⁹ and the Human Population Laboratory⁴⁰ instruments, respectively. At 6 years, the Home Screening Questionnaire (HSQ)³¹ was completed by the primary caregiver to measure the child's home environment. The HSQ consists of 34 questions regarding the physical home environment, parent-child interaction, discipline methods, and variety of stimulating materials and toys in the household. The questionnaire is designed for low socioeconomic status families and is written at a third to fourth grade reading level. The internal consistency and test-retest reliability coefficients are 0.80 and 0.86, respectively. Nutrition was assessed by the total recommended daily allowance⁴¹ of the four major food groups (dairy, protein, fruits/vegetables, and grains) consumed by the child. Information about the intake of each of the food groups was provided by the caregiver. The recommended daily allowance ranged from 0 (did not meet the recommended level for any of the four major food groups) to 4 (met the criteria for all four groups).

Data Analysis

Bivariate analyses were applied first to determine the shape and strength of the association between prenatal marijuana exposure and child's performance on the SBIS at age 6. Multivariate analyses were then used to control for significant covariates. The composite score and each area score were analyzed separately to determine whether the effects of PME on cognitive development were

specific to a certain area. Each trimester of pregnancy was analyzed separately to assess the differential impact of exposure at different times during pregnancy.

A comparison of average SBIS scores at different levels of marijuana exposure was used to examine whether PME was linearly related to SBIS. In addition, the nonlinear model $SBIS = \alpha - \beta \cdot \tanh(\gamma \cdot ADJ - \delta) + \text{error}$, where \tanh denotes hyperbolic tangent function, was fitted to the data. This function is flexible and, based on the estimated parameters α , β , γ , and δ , can resemble either a step function or a straight line.⁴² A step function indicates a threshold effect, whereas a straight line indicates a dose-response relation. This function can also indicate at what level of exposure the threshold occurs. The threshold is estimated by the ratio of δ/γ . S-plus nonlinear least-squares minimization program⁴³ was used to estimate these parameters. The fitted model was then plotted to assess the shape of the relation between PME and the SBIS.

Potential variables considered for inclusion in the model were selected based on the literature and on their association to the SBIS in the MHPCD cohort. These variables included maternal variables (cognitive ability; age at delivery; ethnicity; current level of education; income; work status; marital status; depression; hostility; social support; number of life events; and current use of marijuana, alcohol, tobacco, and cocaine), environmental measures (total number of people in the household, presence of a man in the household, drug and alcohol problems of the man in the household, and current home environment), child variables (sex, nutrition, number of siblings, poor speech/vision/hearing, number of injuries, hospitalizations, and illnesses; and prenatal exposures to alcohol, tobacco, and cocaine).

To reduce the number of covariates, only variables that were related to the SBIS at an α level of .05 (equivalent to zero order correlation of 0.07) were included in the model. A stepwise multiple regression was used to assess the contribution of PME to the prediction of offspring SBIS while controlling for other significant covariates. In addition to the magnitude of the effect (regression coefficient) and its significance, the percentage of variation explained by each variable in the regression model (R^2) is given to illustrate the relative contribution of PME in explaining the total variation in the outcome.

The regression assumptions were examined by plotting the regression errors versus the predicted

values.⁴⁴ Cases with large SEs were suspected of being outliers, and the modified Cook's distance was used to measure the influence of each case on the regression line. One outlier was identified. In this case, the child's composite score was much higher than expected relative to maternal cognitive ability. Because exclusion of this case did not alter the results, the subject was not removed from the analyses.

RESULTS

Forty-four percent of the women (284/648) reported marijuana use at any time during pregnancy. To describe the distribution of use at each trimester, women were categorized as abstainers, those who smoked less than one marijuana cigarette per day (light/moderate users), and those who smoked one or more marijuana cigarettes per day (heavy users). The frequency of prenatal and current marijuana use based on these categories is shown in Table 2. In general, women decreased their use after recognition of pregnancy except for 16 women (2.5%) who initiated marijuana use while in their second and third trimester of pregnancy. On average, first-, second-, and third-trimester heavy users smoked 2.3, 2.0, and 2.4 marijuana cigarettes per day, respectively. Although marijuana use between trimesters was moderately correlated, ranging from 0.56 to 0.64, the pattern of use was not consistent. Only one third of women who reported smoking at the rate of one or more marijuana cigarettes per day during the first trimester of pregnancy continued to smoke at this rate during the later part of their pregnancy, and only 53% of second-trimester heavy users ($ADJ \geq 1$) smoked at that rate during the third trimester of pregnancy.

TABLE 2
Prevalence of Marijuana Use (%)

Time of Assessment	Abstainer	Light/Moderate	Heavy Users	N ^a
Prepregnancy	48.0	30.7	21.3	648
First trimester	58.6	27.0	14.4	648
Second trimester	77.4	17.5	5.1	588
Third trimester	81.5	13.6	4.9	648
6 y	77.6	18.5	3.9	648

Note: Abstainer = no use; light/moderate = more than 0 and less than one marijuana cigarette per day; heavy = one or more marijuana cigarettes per day.

^a Sample sizes differ due to missing data.

TABLE 3
Mean Stanford-Binet Scores by Levels of Prenatal Marijuana Exposure

	Group 1: Abstain (<i>n</i> = 380)	Group 2: Light/Moderate (<i>n</i> = 175)	Group 3: Heavy (<i>n</i> = 93)	<i>p</i> ^a
First-trimester use				
Composite score ^{b,c}	92	93	87	.001
Verbal reasoning ^{b,c}	101	102	96	.000
Quantitative reasoning ^c	94	95	90	.03
Abstract/visual reasoning	85	86	82	.06
Short-term memory ^c	92	95	89	.009
Second-trimester use				
	Group 1: Abstain (<i>n</i> = 455)	Group 2: Light/Moderate (<i>n</i> = 103)	Group 3: Heavy (<i>n</i> = 30)	<i>p</i> ^a
Composite score ^{b,c}	92	92	84	.007
Verbal reasoning ^{b,c}	101	101	94	.01
Quantitative reasoning ^{b,c}	94	94	84	.008
Abstract/visual reasoning	85	85	81	.22
Short-term memory ^c	93	94	86	.05
Third-trimester use				
	Group 1: Abstain (<i>n</i> = 528)	Group 2: Light/Moderate (<i>n</i> = 88)	Group 3: Heavy (<i>n</i> = 32)	<i>p</i> ^a
Composite score ^{b,c}	92	93	86	.03
Verbal reasoning	101	101	96	.12
Quantitative reasoning ^{b,c}	94	96	85	.02
Abstract/visual reasoning	85	86	82	.45
Short-term memory	92	95	88	.07

Note: Abstainer = no use; Light/Moderate = more than 0 and less than 1 marijuana cigarette per day; Heavy = 1 or more marijuana cigarettes per day.

^a Overall significance using *F* test.

^b Group 1 differed significantly from group 3 based on Tukey multiple comparison test.

^c Group 2 differed significantly from group 3 based on Tukey multiple comparison test.

A comparison of women who used marijuana during pregnancy (*n* = 284) with women who abstained (*n* = 364) showed that marijuana users, on average, had lower mean monthly family incomes at the first interview (\$403 versus \$483, *p* < .001) and at 6 years postpartum (\$1,101 versus \$1,251; *p* < .05) compared with the abstainers. Users were more likely than abstainers to be single (25% versus 38%; *p* < .001). Marijuana users scored lower on the WAIS-R than abstainers (86.7 versus 89.8; *p* < .001) and provided poorer home environments as measured by the HSQ (38.8 versus 40.7; *p* < .001). Women who used marijuana during pregnancy were also significantly more likely to report using alcohol, tobacco, and cocaine prenatally and at 6 years than the women who abstained during pregnancy. At the fourth prenatal month, 75%, 64%, and 6% of marijuana users used alcohol, tobacco, and cocaine, respectively, compared to 56%, 46%, and 2% among those who abstained. Fifty-one percent of

alcohol users did not use marijuana and 47% of tobacco users did not use any marijuana during pregnancy. Therefore, although there was overlap between substances, it was not complete.

The average SBIS test scores across different levels of PME are presented in Table 3. Bivariately, the composite scores of children exposed to heavy use (ADJ ≥ 1) during any trimester of pregnancy were significantly lower than the scores of children of abstainers and light/moderate users. Heavy exposure to marijuana during gestation was also significantly associated with poorer performance on the verbal and quantitative reasoning and short-term memory subscales. There were no significant differences between PME groups on the abstract/visual reasoning subscale.

Prenatal marijuana exposure expressed as a continuous variable was significantly correlated with child's IQ. The correlations between the SBIS composite score

at age 6 and first-, second-, and third-trimester marijuana use were -0.13 , -0.12 , and -0.09 , respectively. However, as can be seen from Table 3, the means of the SBIS composite and area scores across different levels of prenatal marijuana use were not linear. The children of light/moderate users did not score differently from the children of abstainers on any of the outcome variables. The fitted hyperbolic tangent function also portrayed a nonlinear relation (Fig. 1). The best fitted estimates indicated a threshold effect at ADJ of 1, 0.7, and 1 for the first, second, and third trimesters, respectively. Therefore, for the regression analyses, these two groups were combined and compared to heavily exposed children.

In the regression analyses, second-trimester heavy marijuana exposure was significantly associated with the child's SBIS composite score after controlling for other

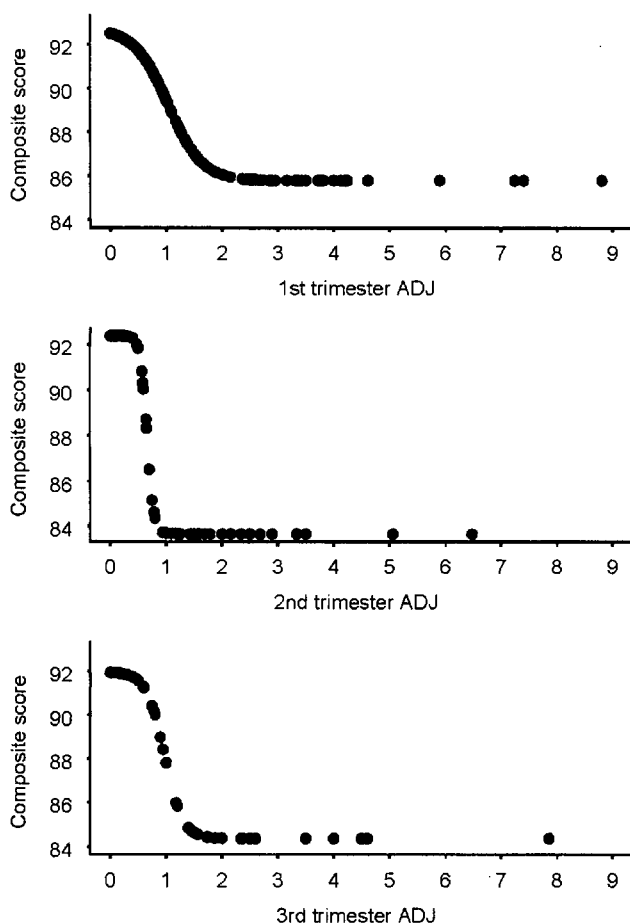


Fig. 1. Fitted hyperbolic tangent function between prenatal marijuana exposure and Stanford-Binet Intelligence Scale composite score. ADJ = average daily "joints" of marijuana. The scale on the y axis represents SBIS composite scores.

predictors. The magnitude of the effect was a 5-point deficit in the composite score (Table 4). First- and third-trimester exposures were not significantly associated with the SBIS composite score once home environment and demographic differences were taken into account.

Additional significant predictors of the composite score included maternal cognitive ability, social support, race, number of people in the household, home environment (HSQ), alcohol problems of the man in the household, number of child's illnesses, and maternal depression. Fifteen percent of the total variation in the composite score was explained by maternal cognitive ability. Other predictors combined explained 8.5% of the variation, and PME explained an additional 1% of the variation in the SBIS composite score. Current maternal marijuana use was not related to the SBIS scores. The average SBIS composite scores among the offspring of current abstainers, light/moderate users, and heavy users were 92.0, 90.1, and 90.7 ($p = 0.4$), respectively.

First-trimester heavy marijuana exposure was significantly related to verbal reasoning, resulting in a deficit of 2.6 points (Table 4). Heavy prenatal marijuana use during the second and third trimesters of pregnancy significantly predicted performance on the quantitative reasoning subscale while controlling for other predictors. The magnitudes of the effects were 8 and 5 points, respectively. Second trimester heavy marijuana exposure was also significantly associated with a decreased score on the short-term memory subscale in the regression analysis (coefficient = -4.5).

We previously reported that PME was not a significant predictor of the child's composite score at age 3 for the total cohort.¹ The current analyses showed that PME was a significant predictor of the composite score at age 6 for the total population. To examine whether there was an overall change in children's IQ from ages 3 to 6 years in the cohort in general, and among PME children in particular, a repeated-measures analysis was conducted. The composite score of second trimester heavily exposed ($ADJ \geq 1$) children decreased by an average of 7.5 points between ages 3 and 6, compared to a change of 3.6 points among nonexposed or lightly exposed children. In the repeated-measures analysis, both heavy PME and time were significant ($F_{1,541} = 10.1$, $p < .01$ and $F_{1,542} = 24.9$, $p < .001$, respectively). The PME by time interaction was only marginally significant ($F_{1,542} = 3.0$; $p < .1$). This means that although heavily exposed children performed more

TABLE 4

Regressions on the Stanford-Binet Intelligence Scale (SBIS) in Which Prenatal Marijuana Exposure Was a Significant Predictor

SBIS Subscale	Significant Predictors	Coefficient ^a	R ²
Composite score	Maternal cognitive ability	0.30***	0.15
	Social support	0.94***	0.03
	Race ^b	3.63**	0.02
	No. of people in household	-0.62*	0.01
	Home Screen Questionnaire	0.25**	0.01
	Alcohol problems of man in household ^c	-3.19*	0.005
	No. of illnesses	0.77*	0.005
	Maternal depression	-0.10*	0.005
	Heavy marijuana exposure ^d		
	First trimester ^e	-1.76	NS
	Second trimester	-5.04*	0.01
	Third trimester	-1.99	NS
Verbal reasoning	Maternal cognitive ability	0.25***	0.16
	No. of siblings	-2.16***	0.04
	Race	3.11***	0.03
	Social support	1.69***	0.02
	Home Screen Questionnaire	0.22**	0.01
	Heavy marijuana exposure		
	First trimester	-2.63**	0.01
	Second trimester	-2.85	NS
	Third trimester	-1.03	NS
Quantitative reasoning	Maternal cognitive ability	0.26***	0.07
	Social support	1.50***	0.03
	No. of illnesses	1.42**	0.01
	Alcohol problems of man in household	-4.48**	0.01
	Race	3.03*	0.005
	Maternal depression	-0.13*	0.005
	Heavy marijuana exposure		
	First trimester	-1.77	NS
	Second trimester	-8.18**	0.01
	Third trimester	-5.35*	0.005
Short-term memory	Maternal cognitive ability	0.29***	0.09
	Home Screen Questionnaire	0.29**	0.02
	Social support	1.59**	0.01
	No. of illnesses	1.11**	0.01
	Poor speech/vision/hearing ^c	-2.73*	0.005
	Heavy marijuana exposure		
	First trimester	-1.47	NS
	Second trimester	-4.51*	0.005
	Third trimester	-2.38	NS

Note: NS = not significant. * $p < .05$; ** $p < .01$; *** $p < .001$.

^a Regression coefficient represents the magnitude of effect per unit change.

^b White = 1, African American = 0.

^c Problem exists = 1, no problem = 0.

^d Heavy exposure = 1, all others = 0.

^e Each trimester was analyzed separately but all are presented together for convenience.

poorly than others and there was a downward change in the composite score in general from 3 to 6 years, the magnitude of change among heavily exposed children was marginally significantly steeper than that of the comparison group of offspring of nonexposed or lightly exposed children. The PME \times race interaction was also tested to examine whether the influence of PME on the SBIS test performance differed by race and it was not significant.

At age 3, we reported that preschool/day care attendance had a significant and positive impact on a child's IQ.¹ In a separate regression analysis, we tested whether preschool attendance continued to predict child's IQ at age 6 and whether the observed effects of PME on SBIS test performance were altered by inclusion of preschool/day care attendance at age 3 in the model. On average, the composite score of children who attended preschool was 3 points higher than those who did not attend preschool, after controlling for other significant predictors ($p < .01$). PME remained a significant predictor of child's IQ at age 6 with preschool attendance included in the model and the effect size did not decrease. Because information about preschool/day care attendance was missing at the 6-year phase for 43 children, this variable was not included in the final model for the current analyses.

DISCUSSION

Children who were prenatally exposed to marijuana at the level of 1 or more marijuana cigarettes per day had lower intelligence test scores at age 6 than their nonexposed peers, controlling for significant covariates. Exposure during the first trimester of pregnancy was related to a deficit in verbal reasoning; second-trimester exposure was associated with lower scores on the composite, short-term memory, and quantitative reasoning subscales; and PME during the third trimester of pregnancy also predicted lower scores on the quantitative reasoning measure. The observed deficits were not linear but were associated with heavy use defined as one or more marijuana cigarettes per day.

The large sample size in the MHPCD study provided adequate statistical power to detect even small effects of PME on the SBIS, while controlling for prenatal exposure to other drugs such as alcohol, tobacco, and cocaine and for the social and environmental factors. A large proportion of variability in child

IQ was explained by maternal cognitive ability, whereas the additional variance explained by the social and environmental factors was small. After controlling for these risk factors, PME explained a small but significant portion of the performance on the SBIS measures of child intelligence.

The effect sizes of PME, although small, were comparable to the effect sizes of other predictors. After adjusting for other predictors, the SBIS composite score of children exposed to one or more marijuana cigarettes during the second trimester of pregnancy was 5 points lower than their nonexposed or more lightly exposed peers, a deficit that is greater than the error of measurement.

These findings are of concern, but they do not by themselves demonstrate causality. The inability to randomly assign subjects to treatment groups is an inherent limitation of human studies, and it is not possible to eliminate all of the sources of differences between the exposed and unexposed groups or to fulfill experimental criteria, such as Koch's postulates, that demonstrate causality. Epidemiological studies use other criteria to impute causality, including biological plausibility, strength of association, consistency, dose-response relationships, and specificity.

With respect to biological plausibility, we noted in the Introduction that laboratory studies have demonstrated a direct effect of PME on the developing brain. The dose and the mode of administration in these studies differed from those of the women during pregnancy and we cannot make a direct comparison. Nonetheless, they provide confirmatory biological evidence of an association between PME and cognitive functioning.

We previously reported a significant association with PME and cognitive functioning among African American children at age 3 in this cohort, whereas preschool and day-care attendance ameliorated the effect of PME among the white 3-year-olds. At the 10-year phase,⁴⁵ we found significant negative effects of PME on the design memory and screening index scores of the Wide Range Assessment of Memory and Learning⁴⁶ and the exposed children had lower school achievement test scores.⁴⁷ Thus, we have found a consistent pattern of effects on cognitive abilities across the phases of the study. The cognitive domains that were associated with PME in our cohort parallel those found by the OPPS at age 4.¹⁷

In our study, the observed effects were associated with heavy use. This lack of linearity has also been reported

by the OPPS, in which effects of PME on offspring cognitive functioning at 3 to 4¹⁷ and 13 to 16⁴⁸ years were only found among offspring of heavy users. Other studies, as we noted in the introduction, did not find effects of PME. This may be associated with different measures, smaller sample sizes, or differing levels of marijuana use. Predictors of performance on the SBIS, such as maternal IQ, social support, and preschool attendance, were the same as other researchers have reported,^{26,27} which also supports the validity of our results.

Thus, although we cannot make direct causal statements using the same criteria as laboratory experiments, we are able to demonstrate that these results are biologically plausible and the associations are significant, demonstrating strength of association. There is consistency between our results and the results of other studies, as well as consistency across phases within our study, and the effects are specific to certain domains, a finding that was also reported by the OPPS.

Second-trimester PME was the best predictor of lower IQ scores. However, 24 of 30 of the second-trimester heavy users also used marijuana heavily in the first trimester and 16 of 30 used marijuana heavily in the third trimester. The third-trimester effect on quantitative reasoning is likely a reflection of second-trimester exposure because almost all of the women who used marijuana in the third trimester were also second-trimester users and half of the heavy second-trimester users were third-trimester heavy users. Exposures late in the first trimester and in the second trimester are congruent with what is known about brain development including the timing of the development of the endogenous cannabinoid⁴⁹ and opioid systems.⁵⁰ These two systems have been shown in animal research to be affected by PME.^{3,51} The final test of timing during gestation will have to be done using experimental laboratory studies with animal models.

Strengths of this study include high retention rates; a detailed assessment of marijuana, alcohol, tobacco, and other drug use during each trimester of pregnancy and at each follow-up phase; and a comprehensive assessment of factors that influence cognitive development such as home environment, maternal cognitive ability, and sociodemographic characteristics. A potential limitation of the present study is the use of the SBIS as the sole measure of cognitive functioning. Although the SBIS has excellent psychometric properties, high reliability, and

good content and construct validity,² it does not measure more specific aspects of cognition such as learning and memory, problem solving, and concept formation.

In conclusion, we have demonstrated that in this low-income population, there is a significant association between PME at levels of at least one marijuana cigarette per day and deficits in cognitive functioning at age 6. The cognitive deficits related to PME were specific to verbal and quantitative reasoning and to short-term memory. As we indicated previously, the deficits were not only statistically significant but they were also greater than the error of measurement. Deficits in these domains could impair a child's academic functioning. These domains can be improved by scholastic and memory enhancement programs. Early detection of these deficits and educational placement in the early elementary school years may prevent future learning problems.

Disclosure: The authors report no conflicts of interest.

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Prenatal Cocaine and Tobacco Effects on Children's Language Trajectories Lewis BA, Kirchner HL, Short EJ, Minnes S, Weishampel P, Satayathum S, Singer LT

Objective: The objective of this study was to examine the effects of prenatal cocaine and polydrug exposure on language development of preschool children using a prospective longitudinal model, controlling for confounders. **Methods:** Children who were exposed to cocaine in utero ($n = 209$) and nonexposed children ($n = 189$) were followed prospectively at birth and at 1, 2, 4, and 6 years of age and were compared on receptive, expressive, and total language scores across time using random coefficient models, controlling for confounders. **Results:** A significant, stable effect of cocaine exposure on language development was observed over time for all language domains, with cocaine exposure related to poorer language performance. Cigarette exposure was related to lower receptive language scores. Environmental influences on language scores were also observed. Both the cocaine-exposed and nonexposed children declined in language performance over time. **Conclusions:** Prenatal cocaine exposure has a stable negative effect on language skills during the first 6 years of life. Both cocaine-exposed and nonexposed children showed decreased language growth over time; however, cocaine-exposed children demonstrated linguistic deficits compared with nonexposed peers and did not catch up. Cigarette and environmental influences were also noted. Reprinted with permission from *Pediatrics* 2007;120(1):e78–85 by the AAP.

Altered Resting Cerebral Blood Flow in Adolescents With In Utero Cocaine Exposure Revealed by Perfusion Functional MRI Rao H, Wang J, Giannetta J, Korczykowski M, Shera, D, Avants BB, Gee J, Detre JA, Hurt H

Objectives: Animal studies have clearly demonstrated the effects of in utero cocaine exposure on neural ontogeny, especially in dopamine-rich areas of cerebral cortex; however, less is known about how in utero cocaine exposure affects longitudinal neurocognitive development of the human brain. We used continuous arterial spin-labeling perfusion functional MRI to measure the effect of in utero cocaine exposure on resting brain function by comparing resting cerebral blood flow of cocaine-exposed adolescents with non-cocaine-exposed control subjects. **Patients and Methods:** Twenty-four cocaine-exposed adolescents and 25 matched non-cocaine-exposed control subjects underwent structural and perfusion functional MRI during resting states. Direct subtraction, voxel-wise general linear modeling, and region-of-interest analyses were performed on the cerebral blood flow images to compare the resting cerebral blood flow between the 2 groups. **Results:** Compared with control subjects, cocaine-exposed adolescents showed significantly reduced global cerebral blood flow. The decrease of cerebral blood flow in cocaine-exposed adolescents was observed mainly in posterior and inferior brain regions, including the occipital cortex and thalamus. After adjusting for global cerebral blood flow, however, a significant increase in relative cerebral blood flow in cocaine-exposed adolescents was found in anterior and superior brain regions, including the prefrontal, cingulate, insular, amygdala, and superior parietal cortex. Furthermore, the functional modulations by in utero cocaine exposure on all of these regions except amygdala cannot be accounted for by the variation in brain anatomy. **Conclusions:** In utero cocaine exposure may reduce global cerebral blood flow, and this reduction may persist into adolescence. The relative increase of cerebral blood flow in anterior and superior brain regions in cocaine-exposed adolescent participants suggests that compensatory mechanisms for reduced global cerebral blood flow may develop during neural ontogeny. Arterial spin-labeling perfusion MRI may be a valuable tool for investigating the long-term effects of in utero drug exposure. Reprinted with permission from *Pediatrics* 2007;120(5):e1245–1254 by the AAP.



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